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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/563,110	06/19/2006	Hanne Muller	Q92287	1130

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EXAMINER	
BETTON, TIMOTHY E	
ART UNIT	PAPER NUMBER
1627	

NOTIFICATION DATE	DELIVERY MODE
11/24/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/563,110	MULLER ET AL.	
	Examiner	Art Unit	
	TIMOTHY E. BETTON	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-29 and 33-44* is/are pending in the application.

4a) Of the above claim(s) *19,20,22,23,25,26,28,29,34,35 and 38-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18, 21, 24, 27, 33, 36-38 and 44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 22 October 2010 has been entered.

Applicants' set of remarks filed on 22 October 2010 has been acknowledged and duly made of record.

Response to Arguments

The crux of applicants' arguments are drawn principally to a passage in the Yazawa et al. reference which suggests that methanotrophic bacterial phospholipids do not comprise any significant amount of EPA. Further, applicants' purport that one skilled in the biomass of Lang is rendered ineffectual in view of the teachings of Yazawa et al.

Still further in alleged support of the above argument, applicants' assert the references of record are not sufficient in order to overcome the general thinking that administration of saturated or monounsaturated fatty acids are believed to be increasers in cholesterol levels.

Applicants' arguments are considered but are not found persuasive because the thrust of the invention is drawn to a method of treatment to reduce plasma cholesterol levels of an animal.

Yazawa et al. teach [that] [t]he eicosapentaenoate-containing phospholipids such as phosphatidylethanolamine and/or phosphatidylglycerol or microorganisms or algae

producing them are used in feeds. Spontaneously hypertensive rats were fed a diet containing phosphatidylethanolmaine and phosphatidylglycerol (manufactured by fermentation of Alteromonas putrefaciens SCRC 2874) for 4 wk to show lower blood pressure, less fat accumulation, and **lower hepatic and plasma triglyceride levels than those fed on control diet.**

Furthermore and of the most distinct importance is the fact that the Makula reference fully encompasses and further strengthens the motivation to combine with Lang and Yazawa as the PE's taught by both references could reasonably be interchanged with the PE's as taught by Makula. The fact that animals are being fed PE food-stuff (biomass) and that Yazawa has clearly pointed out the benefits of such as having anti-cholesterolemic effects further makes the claimed invention obvious. Sanigorski further explains the benefit of the administration of EPA extracted from PE biomass in the way of reducing cholesterol in animals. Applicants' purport that Makula does not teach the benefits of such administration even though it contains each and every element of the alleged invention but the motivation has been clearly elucidated *supra* via the teachings of Yazawa and Sanigorski.

In conclusion, applicants' sole focus on the teachings of Yazawa et al. is deficient in as far as the Makula and Koffas references have been incorporated in order to make obvious the issue as disclosed *supra*.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 18, 21, 24, 27, 33,36-38 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lang et al. Biomineralization of Magnetosomes in Bacteria: Nanoparticles with Potential Applications, printed pages 107-121 and Sanigorski et al. (Platelet and aorta arachidonic and eicosapentaenoic acid levels and in vitro eicosanoid production in rats fed high-fat diets, Lips. 1996 Jul; 31(7): 729-35. and Yazawa et al (Eicosapentaenoic acid-containing phospholipids for Feeds 1992, Jpn. Kokai Tokyo Koho, 5 pp. in view of Makula et al. (as already made of record) and Koffas et al. (2002/0137190 A1).

Lang et al. is employed to show evidence of the abundance of phosphatidylethanolamine identified in extracts of the magnetosome membrane from *M. gryphiswaldense,* which is a biomass (page 111, 2nd column, 2nd paragraph). The phrase, "*most abundant polar lipid[.]*" would reasonably constitute to the one of skill, a percentage of microbial lipid comparable to

80%wt (please see claim 36).

Lang et al. does not teach whereby plasma cholesterol levels are reduced.

However, Yazawa et al. teach [that] [t]he eicosapentaenoate-containing phospholipids such a as **phosphatidylethanolamine** and/or phosphatidylglycerol or microorganisms or algae producing them are used in feeds. Spontaneously hypertensive rats were fed a diet containing phosphatidylethanolmaine and phosphatidylglycerol (manufactured by fermentation of Alteromonas putrefaciens SCRC 2874) for 4 wk to show **lower** blood pressure, less fat accumulation, and **lower** hepatic and **plasma** triglyceride levels than those fed on **control** diet (abstract only).

Thus, Yazawa et al. establishes the nexus as to reasoning drawn to phosphatidylethanolamine and eicosapentaenoate (EPA), which is well-known in the art as an anticholesterolemic component.

Yazawa et al. does not teach the direct correlation directed to reducing cholesterol.

However, Sanigorski et al. teach the reasoning as to why it would be obvious to extract the lipids of Lang et al. which is further defined by Yazawa et al. as an eicosapentaenoate-containing phospholipid (EPA). EPA is art-known as a component in dual therapy with DHA in order to treat hypercholesterolemia. Sanigorski et al. teach the beneficial effects of the administration of EPA in animals administered this high-fat diet. Please see below:

> There is a significant interest in the interrelationship between long-chain n-3 and n-6 fatty acids due to their ability to modulate eicosanoid production. In general, the intake of arachidonic acid (AA) results in enhanced eicosanoid production, whereas n-3 polyunsaturated fatty acids (PUFA) decrease the production of eicosanoids from AA. **The purpose of this study was to investigate whether the effects of dietary AA on eicosanoid production in the rat were correlated with the AA and EPA levels in platelets and aorta (eicosanoid-producing tissues). Four groups of male Sprague-Dawley rats were fed a high-fat diet enriched with eicosapentaenoic acid (EPA)** and docosahexaenoic acid (DHA) (approximately 100 mg/day of EPA + DHA) for 24 d. During the last 10 d, the four groups were orally supplemented with 0, 30, 60, and 90 mg/day of ethyl arachidonate. A further group of rats was

> fed a control diet (without long-chain n-3 PUFA) for 24 d. In vitro aorta prostacyclin (PGI2) production, serum thromboxane A2 (TxA2) production and plasma, and platelet and aorta phospholipid (PL) fatty acids were measured. Enriching the diet with n-3 PUFA resulted in significant reductions in tissue AA levels and an increase in the n-3 PUFA, particularly EPA. On this diet, the AA to EPA ratio was 1:1 in platelet PL, and it was 2:1 in the aorta PL. There were significant decreases in the in vitro PGI2 and TxA2 production compared with the control animals. The inclusion of AA in the diet resulted in marked increases in AA levels in the platelet and aorta PL with corresponding decreases in EPA. The lowest dose of AA (30 mg/rat) reversed the effects of 100 mg/day of n-3 PUFA on AA levels in platelet and aortic PL and on in vitro aorta PGI2 and serum TxA2 production. The dietary AA caused a differential (twofold) increase in TxA2 relative to PGI2 for all three levels of AA supplementation. There were greater changes in the levels of AA and/or EPA in platelet PL compared with the aorta PL, which might have accounted for the differential effects of these PUFA on thromboxane production compared with PGI2 production in this study (printed pages 1 and 2, entire).

Accordingly, Makula teaches phospholipids of Methylococcus capsulatus, Methylosinus trichosporium, La Paz, and OBT were examined in relation to their qualitative and quantitative composition. M. Capsulatus exhibited a phospholipid composition consisting of **phosphatidylethanolamine**, phosphatidylglycerol, cardiolipin, and phosphatidyl-choline. The esterified fatty acids were predominantly C16:0 and C16: 1. M.trichosporium, La Paz, and OBT exhibited an essentially identical phospholipid composition consisting of phosphatidylmonomethylethanolamine, phosphatidyl-dimethylethanolamine, phosphatidylcholine, and phosphatidylglycerol. Only trace amounts (less than 1%) of cardiolipin were found in these organisms. The major esterified fatty acid in these organisms was C18: 1 (87 to 90%). The monounsaturated fatty acids from all four organisms consisted of both cis and trans isomers, each of which contained delta8, delta9, delta10, and delta11 double-bond positional isomers (Abstract only).

As disclosed above, Makula teaches phospholipids of Methylococcus capsulatus, Methylosinus trichosporium.

Makula et al. teach phosphatidylethanolamine, phosphatidylglycerol, cardiolipin, and phosphatidyl-choline.

Additionally, Makula et al. teach esterified fatty acids as being predominantly C16:0 and C16: 1.

Makula does not teach administration to fish or juvenile fish. Makula also does not teach a utility for phosphatidylethanolamine.

However, Koffas et al. (2002/0137190 A1) teach [...] different livestock animal types may have different nutritional requirements in terms of the relative proportions of protein to carbohydrate. Many carnivorous aquatic **fish** species, for example, have very high protein requirements. Ruminant livestock, on the other hand, thrive on higher fiber/carbohydrate diets. Methylomonas 16a has the capacity to form large amounts of carbohydrate, under certain conditions, in addition to the cellular protein which is always produced. Genes involved in gluconeogenesis (glycogen formation) or glycogen degradation might be altered or regulated such that glycogen content could either be decreased or increased. Thus the composition of the crude cell mass could be modulated to target high protein markets (lower carbohydrate) or alternatively, higher carbohydrate lower protein feed markets. **The ability to engineer the composition of the microbe precludes the need to artificially formulate protein/carbohydrate ratios by exogenous additions** [0156].

Further Koffas et al. (0137190 A1) teach methods of administration [that] the present invention provides a unique methanotrophic bacterial strain, useful for the production of a variety of materials from C1 carbon sources such as methane and methanol. The strain is referred

to herein as Methylomonas 16a, and is characterized by rapid doubling time, high yield and the presence of genes encoding both the Entner-Douderoff carbon pathway as well as the Embden-Meyerhof pathway, allowing for versatility in carbon flux management and higher efficiency of carbon incorporation. The strain has been shown to produce a variety of food and feed products such as single cell protein, exopolysaccharide and starch. The strain has particularly high value in the production of food and feed materials as it is possible to manipulate the various concentrations of protein, carbohydrate and starch all within the same organism. **This capability will permit strains to be uniquely tailored for individual specific food and feed applications.** Additionally the strain has demonstrated utility in the production of terpenoid and carotenoid compounds, useful as pigments and as monomers in polymeric materials [0075].

Koffas et al. (0137190 A1) does not teach juvenile fish, however it is obvious based in the context of the teachings that any fish would have at one time been a juvenile fish being administered these same food and feed formulations.

Determining the scope and content of the prior art, instant claim 18 discloses nothing with regard to the extraction of a lipid component as cited in the current set of arguments. The method is directed to no specific target population/ classification of fish (as elected) or animal. Claim 18 is broad and not exclusive with regard to the target population treated. Thus, any reference teaching the feeding of PE to animals would be expected to achieve the same effects as taught in the invention. Phosphatidylethanolamine is abundant in a cell mass (biomass), which reasonably overcomes the limitation of claim 36.

In ascertaining the differences between the art and the claims at issue, the art teaches variable species of biomass and does not expressly equate the lipid extract of said biomass as being beneficial in reducing hypercholesterolemia. However, the references *supra* adequately address the limitations drawn to a method of treatment to reduce plasma cholesterol levels based upon the reasoning of Yazawa et al. Further, the teachings of Makula et al. could reasonably be extended to microbial lipids based upon obviousness to try further modulation/extraction of lipid components in the normal course of due experimentation.

Objective evidence present in the application is drawn to a phospholipid which is abundant as an extract of crude cell mass. Yazawa et al. teach utility [that] [t]he eicosapentaenoate-containing phospholipids such a as **phosphatidylethanolamine** [...] are used in feeds. Lang et al. does not teach PE as being eicosapentaenoate-containing but based upon the plethora of nutrients to be extracted from a biomass as described in Lang et al. and in the general prior art, EPA could be reasonably interpreted as an element that may be magnetically aggregated. Sanigorski et al. establishes the beneficial effects of EPA-containing phospholipid such as PE as Yazawa establishes that the subject that may benefit may be marine life, (i.e., fish), but is also not exclusive to marine life.

Overall obviousness is reasonably recognized based upon what is clearly taught by the general biomass of Lang et al., which may be extended to include a plethora of variable nutrients as disclosed. Based upon Lang et al., Yazawa et al. provides further motivation by teaching PE which may be used in feeds. Sanigorski et al. provides reasoning as to why the teachings of Lang et al. could be extended to include the teachings of Yazawa. The procedure of extracting the biomass of Lang et al. would reasonably aggregate EPA containing phospholipids (as taught by

Yazawa). This, in turn, would reasonably result in a perceived lowering in the cholesterol levels of said subjects having any form of ingestion of the particular component. Absent of any distinction or delineation clearly pointing out that this particular PE as claimed is essentially free of any form of EPA (a known natural component to palliate hypercholesterolemia), instant obviousness should be reasonably apparent to the one of skill.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY E. BETTON whose telephone number is (571)272-9922. The examiner can normally be reached on Monday-Friday 8:30a - 5:00p.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

TEB

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627